THE HORMONES

And Their Control of the Reproductive System

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HORMONES controlling reproduction can be defined in a wide and in a narrow sense. Obviously, every hormone which affects the constitution and the general functions eventually affects reproduction. For example, thyroxin decreases the viability of rats in high temperatures; and hyperthyroid individuals will be less fertile than normal animals in a habitat of high temperature. These general effects of many hormones necessitate a restriction of the discussion to those which specifically influence reproduction. Even so, a short review cannot do more than just outline some of the problems and results of recent research.

The case of the male hormones is comparatively simple, but perhaps only because we as yet know little about them. It had been known since pre-historic times that removal of the testicle before puberty prevented the full development of maleness. Then Berthold showed that the implantation of a testicle in a capon prevented the atrophy of the comb which usually results from castration; and it is to him that we owe the conception of the endocrine function of the testicle—i.e. the idea that the testicle exerts its effects upon the development of the sexual characters through a substance secreted into the bloodstream.

A long series of researches by many workers has since carried us much farther. The testicular hormone has been extracted from the testicles of various animals, and has actually been shown to produce many of those phenomena which were ascribed to its action when it was only an abstract hypothesis—a feat probably as wonderful as the prediction and discovery of Neptune. For instance, the accessory genital glands, the secretion of which forms the bulk of the ejaculated semen, degenerate and atrophy after castration within a short time. Injection of testicular hormone leads to a regeneration of these glands, which recover their functional activity. The comb of the castrated cock also recovers its normal size and appearance after injections of this testicular hormone. All these effects may seem not so very important in themselves, but they are to be regarded as indications of the activity of the hormone; and they are important since normal comb growth and normal function of the genital glands are usually associated with the other and more important actions of the testicular hormone—such as the induction of the sex instinct, male development of the body, etc.

Apart from its effect on the growth of the prostate and seminal vesicles, the testicular hormone is necessary for the normal function of the epididymis—an organ attached to the testicle and important as a storehouse of spermatozoa. The spermatozoa present in the epididymis lose their motility very soon after the testicles have been removed even if the epididymis has been carefully spared. But animals will remain fecund after such an operation if they are injected with the testicular hormone. Apparently the epididymis gains and retains its ability to provide the necessary conditions for spermatozoa only as long as it is supplied with this hormone. The retention of fecundity under its influence will render a castrated male fertile as long as the store of spermatozoa lasts.

Obviously the motility of the spermatozoa is indirectly determined by, among other factors, the quantity of the supply of hormone. This must be of some importance in relation to the reproductive power of a male, particularly in double or manifold matings, relative fertility being influenced not only by the genetic constitution of the spermatozoa determining motility, but also by the endocrine conditions of the male, which are influenced by many and various environmental factors.

THE INFLUENCE UPON SEX

The action of the male sex hormone offers many more points of interest, quite apart from its influence upon the constitution of the body, which is very considerable; for there is good ground for the assumption that the development of the male form is largely, if not exclusively, dependent on the timely action of the testicular hormone. It also seems that this hormone even has an influence upon the formation of the testicle itself.

As is generally known, in the very early stages of fœtal development, male and female embryos are completely alike, each possessing the rudiments of the genital organs of both sexes. Sex development (or rather differentiation) consists normally in the atrophy of one set and the development of the other. In cattle it sometimes happens that blood-vessels of hetero-sexual twins, male and female, fuse at an early stage. In these cases the female is transformed, more or less completely, into a male or an animal resembling a male in its genital organs. The transformation of these so-called ' freemartins ' is not restricted to the accessory sex characters, but includes also the gonad, which instead of becoming an ovary (as it does in undisturbed female development) develops into an organ resembling a testicle in structure. This transformation of the female twin into a ' freemartin ' is due to the action of the male twin's testicular hormone, which is carried across in the joint blood circulation.

Thus it appears that the testicular hormone also determines the structural organization of the gonad, so that the male gonad is dependent in its development on the action of its own hormone! This may at first sound rather absurd, since it is difficult to understand how the male gonad can develop if it needs its own products to do so. But one must not forget that the testicle is a composite gland, consisting of the tubuli, wherein the spermatozoa are produced, and the interstitial tissue, where the hormone is elaborated. The formation of hormone-producing cells precedes and conditions the development of the spermatogenic elements, which produce the spermatozoa and are thus directly responsible for reproduction. It still remains to be discovered in what degree the production of the hormone in the later phases of life is necessary for, and of influence upon, the production of spermatozoa.

The production of the male hormone influences reproductive processes in many other ways as well. The complicated reflexes which lead to erection and eventually ejaculation also depend on the previous secretion of testicular hormone. But even with all its many influences upon sexuality and reproduction, the hormonic system in the male appears, at least at present, to be much simpler than in the female. Here not one sex hormone, but at least two are involved; and in considering them a somewhat wider biological survey is necessary.

THE HORMONES OF THE FEMALE

In the males of all vertebrates the ejaculation of semen represents sexual as well as reproductive activity. In many fishes the parallel function in the female, the extrusion of the eggs, is equivalent to the ejaculation of semen: it represents both the reproductive and the sexual act of the female. In the higher vertebrates conditions are much more involved. First of all, the sex act in the female no longer consists in an extrusion of its own gametes, but in the reception of the gametes of the opposite sex or in the processes accompanying this reception. The actual reproductive

function in the female of the higher vertebrates starts with the liberation of the ovum, preceded by sexual activity and followed by more intensive reproductive activity—particularly in mammals. This separation of sexual and reproductive functions is very clearly expressed in the behaviour of the genital organs in the great majority of mammals. Not only are there stages of relative rest, when the genital organs do not function at all—this inactivity sometimes lasting the greater part of the year—but the functional stages are clearly divided into a " sexual " and a " reproductive " phase. During the sexual phase, before ovulation, an enlargement occurs in the vagina which during the periods of relative rest is too small to admit the penis. The uterus, which is of small diameter during the phase of sexual rest, undergoes parallel changes—in the rat, for instance, it is filled with a fluid which permits the approach of the spermatozoa to the fallopian tubes and thus to the egg. All these complicated changes are co-ordinated with ovulation, which occurs during their progress; after it has occurred they are neutralized; the fluid from the uterus (again taking the rat as an example) is ejected, the uterus collapses, the special epithelium formed in the uterus and particularly in the vagina is destroyed or thrown off, and the tissues relapse into a more undifferentiated state.

Thus a starting point for a fresh and different activity is reached and made use of. For now begin the changes in the uterus which permit the nidation and development of the egg, conditions being created which are entirely different from those accompanying fertilization and insemination. These pregnancy changes persist and develop until the special structures (decidual elements, etc.) formed during their progress are eliminated in the act of birth or immediately thereafter, when a neutral stage again is reached and the initial conditions of rest are restored.

Thus the changes in the genital organs form a complete cycle, leading back to the point whence they started. It will be realized that this ' sex cycle ' is divided into two phases: the phase of the changes connected with insemination and fertilization to which mating is restricted—the sexual or œstrous phase—and the second phase of changes connected with the creation and maintenance of the conditions of pregnancy—the reproductive phase.

INDUCING PSEUDO-PREGNANCY

The changes in both phases, whether of behaviour ('heat') or anatomical and physiological, are incited by hormones liberated by the ovary. There are at least two such hormones and they are, in mouse and rat, liberated in succession. During the first phase of ovarian secretion, which precedes ovulation, *œstrin* is produced. It is a hormone which has now been prepared in a highly purified state; and some even believe they have produced it in crystalline form free of any impurities. Its injection into ovariotomized mice, in which no sex cycle occurs in the absence of any ovarian hormone, causes the complete series of the œstrous changes. The animals mate under its influence and also display the anatomical conditions of œstrus. During the second phase of ovarian secretion which follows ovulation there is produced another ovarian hormone, *kythin* or *progestin,* which is responsible for the changes in the uterus permissive of pregnancy development. The actions of this hormone are best demonstrated in rats and mice. If one injects *kythin* and then imitates the stimulus exerted by the egg upon the uterine mucosa by irritating it mechanically, the so-called ' deciduomata ' are formed, representing the maternal part of the placenta. But deciduomata are never formed after injections of *œstrin*. *Kythin* not only prepares the uterus for the duties it has to perform during pregnancy, but is also necessary for the maintenance of pregnancy. Removal of the ovaries—the source of *kythin*—leads to abortion; but injections of *kythin* prevents the interruption of pregnancy.

These experiments demonstrate most clearly the influence and role of *kythin,*

which is the pregnancy hormone and thus the reproduction hormone *par excellence*. There is good reason to assume that it is also responsible for the post-partum activities connected with reproduction, such as the display of maternal reflexes and lactation. Its supply to the uterus in sufficient quantities is necessary for the normal development of the embryo, which depends on the functions of the uterine wall or their derivatives for its nutrition.

While the fundamental role of *kythin* is now established, there is still very little known of the actual mechanism of its action. But still, its biological role as the hormone which creates the conditions of reproductive activity in the full sense of the words is established.

'RELIEVING' THE GERM-PLASM

It is perhaps worth while also to mention two points in which *kythin* bears upon general questions. In one sense it acts as a 'reliever' of the germ-plasm. If one had to construct an animal in which internal development occurs—as is the case in mammals—one would have to make sure that the uterus provided for the conditions of development after fertilization had occurred. If this provision depended on the actual occurrence of fertilization, the egg would have to send some message, so to speak, to the uterus, informing it that preparation for pregnancy was necessary. This would involve the elaboration of a hormone on the part of the egg—in other words, a somatic activity of the germ-plasm.

The elaboration of *kythin* in the ovary relieves the egg of this somatic function; moreover, it has been established in a long series of observations and experiments that the elaboration of *kythin* on the part of the ovary is entirely independent of the actual occurrence of fertilization and even not conditioned by the presence of an egg. In other words, the second phase of ovarian function is in all mammals independent of the occurrence of fertilization (though there are some species in which its occurrence depends on accessory factors, such as mating).

While this independence of the *kythin* secretion relieves the germ-plasm of any somatic duties (a situation analogous to that in the male, where also the germ-cells are not involved in the production of a somatically active hormone), the organism pays a heavy price for this relief; for the secretion of *kythin* in the absence of fertilization leads to the occurrence of a stage of pseudo-pregnancy. For some time after ovulation the uterus undergoes all those changes which are characteristic of, and necessary for, the early stages of pregnancy; and in some mammals, such as the bitch of certain marsupialia, the ovary does not realize, as it were, that its efforts are in vain before the normal term of pregnancy has actually passed. These empty pregnancies are, of course, so many 'unnecessary' strains. But while the actual duration of pseudo-pregnancy varies very considerably, and the intensity of its phenomena differs very much, its occurrence is a universal phenomenon—much more so than œstrus, which does not occur in some mammals, such as the primates, including man. Here the anatomical and psychological conditions for sexual activity, once developed, persist and show little or no regular fluctuation. The sexual phase of the cycle is abolished; there is no definite pre-œstrous development, and therefore no process of post-œstrous neutralization, such as occurs in the diaphasic animals, is necessary. The cycle in primates is monophasic and represents, in the main, only a reproductive phase. Thus ovulation is either followed by pregnancy or, in the absence of ovulation, by the vain development of pregnancy conditions—by a pseudo-pregnancy which ends after a few days in a pseudo-birth. The latter is called menstruation owing to the almost accidental fact of its monthly occurrence.

While pseudo-pregnancy is universal among the mammals and is biologically comparable in all of them, its anatomy and physiology are not completely comparable

in the various forms. The anatomical characteristics vary with the particular form of placentation (or absence of placentation), and the mechanism is also different in the various groups of mammals. While the second phase of the cycle (it may be pseudo- or true pregnancy) in the mouse represents an effect of *kythin*—at least there is no indication that any *œstrin* is present in either pseudo- or true pregnancy—it is certain that in other forms, such as the cow or human, the second phase is due to the combined action of both *œstrin* and *kythin*. This needs some explanation, since it is of importance for the understanding of hormonic action.

TWO ANTAGONISTIC HORMONES

One of the effects of *œstrin,* which is an integral part of the œstrous phase of the diphasic cycle, is the incitement of cornification. The vaginal epithelium, which during the period of rest consists of ' low ' cubic cells, undergoes proliferation (an augmentation of cells), and the newly formed cells then become keratinized, forming horny scales. But under the influence of *kythin* those ' low ' cells of the interval stage are transformed into ' high ' mucous cells with great secretory activity. Thus one of two alternative reactions is possible—cornification or mucification. The epithelium can react either way, and if a sufficient amount of *œstrin* is injected when mucification is in progress, the mucified epithelium is destroyed. Vice versa, the injection of a sufficient amount of *kythin* prevents the occurrence of cornification. There is obviously an antagonism between the reactions of the vaginal epithelium to the hormones. The same applies to the reactions of the uterus : *œstrin* prevents or interrupts the pregnancy changes if injected in large quantities, and *kythin* prevents insemination by preventing the oncoming of œstrous changes. Thus it is possible to prevent the occurrence of fertilization by the administration of these hormones, and so negatively to control the processes of reproduction. In monophasic animals conditions are different. In man and monkeys no œstrous phase occurs, and therefore (so to say) *œstrin* is not needed to prepare the uterus and vagina for insemination. Its power to influence the growth of the uterine elements and hyperæmia is therefore utilized in inducing the pregnancy changes in collaboration with *kythin*. Here the reactions of the genital systems to *kythin* and *œstrin* are not alternative, and their effects are not *antagonistic, but synergetic.*

It must be assumed, however, that a certain balance of the hormones is necessary for the progress of pregnancy (or pseudo-pregnancy) on its normal course. It is surprising that similar conditions also apparently prevail in diphasic animals like the cow : but we know as yet too little about the details. All we can say and have to consider is that the differences in the form and nature of the sex cycle, as they occur in various species, are due not only to a difference in the amount and time-coordination of hormone secretion, but also to a difference in the mode of response on the part of uterus, etc. This is obvious although—or perhaps because—there has not yet been time for much research on this fundamental fact.

EXTRA-OVARIAN FACTORS

The story of the ovarian hormones is long enough to fill a day's narration; but it is bound to remain incomplete if it does not refer to the extra-ovarian factors which control the production of ovarian hormones. The existence of such extra-ovarian factors had been assumed for a long time. The English biologist W. Heape postulated the existence of a generative ferment, the presence and concentration of which directed and conditioned gonadic function. It had also been shown that the implantation of an immature ovary into a mature female led to immediate maturation of the graft, which otherwise would have remained immature for some time. Vice versa, the transplantation of a senile, inactive ovary into a mature, still sexually active female was found to lead to a regeneration of the senile

graft. These experiments showed that the beginning and termination of the functional life of the ovary were determined by factors outside the ovary itself; some of them, it should be said, have since been identified.

Thus it has been established that the removal of the pituitary prevents the onset of puberty and retains the ovary in a state of immature inactivity. On the other hand, grafts of the anterior lobe of the pituitary lead to a premature occurrence of œstrus in immature animals. Quite rightly it had been concluded that the anterior lobe is necessary for, and actually incites, the function of the ovary—that it invokes the production of an ovarian hormone. We have, however, to consider a further complication. We cannot speak of " the " ovarian hormone, since we have learned that there are at least two such hormones, which are in many animals, such as mouse or rat, secreted in two distinct phases of ovarian activity. Now, in the absence of a pituitary gland neither phase occurs; but, as has been shown recently, pituitary extracts can incite either phase of ovarian secretion, according to the method of extraction applied. Thus one kind of extract incites œstrus though it has no direct influence upon either uterus or ovary—but it induces the production of *œstrin*. And another kind of extract incites pseudo-pregnancy—again by activating the ovary and inducing *kythin* production. It seems that this difference in effect is due to the relative concentration of two factors of the anterior lobe (*Gonadotropic* hormones or *Rho*-factors as they were called when their existence was deduced hypothetically). It appears that one of these hormones is *œstrogenic*—it induces the formation of *œstrin*. The other one is the hormone responsible for the elaboration of *kythin* on the part of the ovary. Thus one must be regarded as the super-ordinated sex hormone, and the other as the super-ordinated pregnancy hormone. They have been referred to as the *œstrogenic* and *kyogenic* hormones, respectively.

Many experiments with these gonadotropic hormones have already been performed and have produced interesting results. If *kyogenic* extracts are injected into a pregnant mouse, pregnancy is prolonged beyond the normal term, since the extract prolongs secretion of *kythin*. On the other hand, one can prevent pregnancy with the same extracts if one injects them before the œstrous cycle comes on. The extract, by inducing the second phase of ovarian action, prevents the first phase; and the animal becomes pseudo-pregnant before having been in œstrus. On the other hand, the injection of *œstrogenic* extracts prevents the development of the pregnancy changes.

Among the many facts to be deduced from these experiments, some are particularly worth mentioning. It appears, for example, that the sexual periodicity as it occurs in most mammals is ultimately due to a pituitary periodicity, and that pregnancy also is ultimately maintained by pituitary action.

This leads us on to another point of some interest. Both pseudo-pregnancy and pregnancy are due to the same hormone (*kythin*) and differ only in degree; but their duration, in most species, differs greatly—pseudo-pregnancy, as a rule, being much shorter than true pregnancy. This is due, as we can state on the basis of many experiments, to a difference in the duration of *kythin* secretion. Prolonging *kythin* secretion by means of *kyogenic* extracts leads to a prolongation of pseudo-pregnancy to the full extent of true pregnancy or even beyond it. How is it, then, that the actual occurrence of fertilization leads to a prolongation of *kythin* secretion?

The answer is simpler than one might expect. In the mouse, for instance, the placenta produces a *kyogenic* hormone, thus stimulating the ovary and prolonging the production of *kythin*. The placenta, the formation of which depends on the preparation of the uterus by *kythin,* itself prolongs the conditions of its maintenance.

THE CYCLE IN THE PRIMATES

What has been said in the above paragraph applies directly only to the diphasic animal, e.g. the mouse. When we come

to the monophasic animal—man, monkey—things become more difficult. Here both ovarian hormones are involved in the development and persistence of pregnancy conditions, and the production of both must be maintained throughout pregnancy. It accordingly appears that both *gonadotropic* factors are produced by the human placenta. And while it is easy to prevent in the mouse either phase of the cycle by inducing the other phase, it is not possible to do this in the monophasic animal where the hormones work synergetically.

However, the influence of *gonadotropic* hormones is not restricted to the incitement of the production of one or the other ovarian hormone, but also affects phenomena even more intimately connected with reproduction. While no ovulation occurs after the removal of the pituitary gland, grafts of its anterior lobe incite ovulation; and so do *œstrogenic* extracts. The follicles enlarge, burst, and render mature (fertilizable) eggs. A sufficient number of grafts even increases by several hundred per cent. the number of eggs which are liberated by the ovary at any period of ovulation.

But the same influences which thus induce ovulation can prevent its occurrence. It is generally known that the enlargement of the follicle which culminates in ovulation is followed by proliferation of the epithelium which lines the follicle. Finally the cells of this epithelium fill with their proliferated mass the whole cavity of the follicle, having undergone a certain transformation which renders them rich in a substance which gives them a reddish-yellow appearance. The whole body of these cells which replace the follicle—or rather fill it—is called *corpus luteum* (yellow body). It is these cells, by the way, which are richest in *kythin*.

Now, normally the *gonadotropic* hormones are produced at a rate which guarantees the proper sequence in the enlargement of the follicle, its bursting (ovulation), and the luteinization following ovulation. But a considerable increase in the amount of *gonadotropic* hormones leads to very fast luteinization, which is almost complete before the follicle has had time to enlarge and to ovulate. Thus the egg is enclosed in a mass of cells and no ovulation and fertilization are possible.

It appears, therefore, that the same substance which induces ovulation can also prevent it. It is of some interest that experiments show that the same mechanism prevails in monkeys, which are directly comparable with man.

Space does not permit the discussion of the many other phenomena and problems connected with the action of the *gonadotropic* hormones. There is, however, one field which must be briefly touched.

THE MALE PITUITARY GLAND

What has been said of the ovary also applies to the testicle in some degree. Here again we find inactivity after removal of the pituitary gland, and restoration of the function after application of anterior lobe grafts or extracts. Moreover, precocious maturity can be induced by such extracts. On the other hand, it has been shown that the senile decay of the testicle, which is connected with the loss of spermatogenetic power and endocrine activity, can be restored by means of *gonadotropic* hormones. The senile testicle resumes its secretion and again produces spermatozoa, which appear to be perfectly viable. Thus apparently fecundity and testicular secretion also depend on anterior lobe secretion, though it is as yet uncertain whether both *gonadotropic* hormones exert a positive influence upon the testicle. In fact, it seems that the *kyogenic* extracts have a rather detrimental effect upon the testicle.

Doubtless further research will reveal many other important actions of these hormones upon the reproductive system. And having said, in the beginning, that, in a way, all hormones control reproduction, we now must invert the statement and stress the complementary view—that the hormones controlling reproduction in the narrower sense of the word have effects far beyond the reproductive system. It is well known how much they influence constitution—the

comparison between castrates and normal individuals has taught us thus much. Their influence upon the energy-production of the body, upon the mental activities, and upon many other functions of the organism, cannot yet be wholly visualized; but they seem to be of very great importance. Therefore the knowledge of the action of these hormones means much to the physiologist and physician; and we may say that control over the reproductive hormones means much more than control over reproduction.

MR. PUNCH ON EUGENIC FAMILY ENDOWMENT

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THIS strange case, in which the accused are the principal members of the late Conservative Government, was concluded at the Old Bailey to-day.

Mr. Justice Trout, addressing the jury, said: "This painful but important case has revealed a singular story. The prisoners in the dock are indicted at the instance of a Naval officer, Commander Paravane, upon two counts—first, that they did obtain a considerable sum of money by false pretences, and, second, that they did, severally and collectively, libel the Commander.

"Now a number of the officers in His Majesty's Navy are married and have children; and, as you have heard, it is the principle or habit of the State to look with especial favour upon those who take upon themselves the responsibilities of matrimony and parenthood, since, for reasons not wholly clear to all of us, it is still considered desirable that the population of these already over-crowded islands should continually increase. Therefore the taxes exacted from a bachelor are greater than those required of a married man; and the income-tax of a father is reduced, though not extensively, in exact proportion to his fertility. Pensions are granted to widows, but not to spinsters equally needing support. In addition, the officers and men of His Majesty's fighting forces receive higher pay (or allowances) from the day that they lead some happy girl to the altar—that is to say, the officers and men of the Army, the officers and men of the Royal Air Force, and the men (but not the officers) of the Royal Navy. The exception is a startling one. . . .

"It does credit, no doubt, to the heart of the nation that we deny to the officer what we are willing to grant to the simple seaman, but it will not, I think, enhance our reputation for common-sense. Is it to be understood that it is correct and desirable for an ordinary or able-seaman to take a wife, but not for the Captain of his ship? Are the children of a stoker satisfactory additions to the race but not the offspring of an Admiral? Surely we are agreed that the blood and spirit of Nelson and Drake are not confined to the forecastle? 'Hearts,' if I may be permitted to imitate a celebrated poem:

> 'Hearts just as hard to check
> Beat on the quarter-deck,'

and the arguments which support the endowment of marriage in the one place cannot miraculously lose their substance in the other.

"One of the Naval witnesses, a bachelor, ventured to attack the principle itself; but it is too late, or perhaps too early, to do that. If it were accepted